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Further Delineation of the Acro-Renal-Ocular Syndrome

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A triad of acral, renal, and ocular abnormalities was reported previously in four families. We report on a fifth family, in which a mother, one of her four sons and one of her two daughters are affected. Major findings in the acro-renal-ocular syndrome are upper limb abnormalities, mainly thumb hypoplasia, eye abnormalities such as coloboma and Duane anomaly and renal migration defects. A close embryological-temporal relationship between the traits of this entity suggest a common monogenic cause. The pattern of inheritance is probably autosomal dominant. Because of a wide variability of clinical manifestations, recognition of the syndrome in individual cases may be difficult. © 1996 Wiley-Liss, Inc.

KEY WORDS: acro-renal-ocular syndrome, upper limb abnormalities, radial ray defects, eye coloboma, Duane anomaly, renal ectopia, autosomal dominant inheritance

INTRODUCTION

The association of limb and urinary tract defects appears well established. In a population based study of over 1,500,000 Hungarian infants, Evans et al. [1992] reported several specific acrorenal associations, including renal agenesis or dysplasia together with radial ray defects, micromelia and amelia. These authors also found that combined renal and limb anomalies often occur in association with malformations in other systems. Thus, six major malformation groups were identified by cluster analysis. The combination of acrorenal malformations together with ocular anomalies was not mentioned in the review and, hence, seems to be rare.

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Halal et al. [1984] were the first to report on acro-renal-ocular syndrome as a distinct entity. Temtamy and McKusick [1978] had already shortly mentioned a similar family, and later on, Naito et al. [1989] and Pierquin et al. [1991] described two other families. Here we describe a man with upper limb, renal, and ocular abnormalities, whose mother and one of his sisters also have upper limb abnormalities. This family provides further evidence for the existence of the acro-renal-ocular syndrome as a separate monogenic entity.

CLINICAL REPORTS

Patient 1 (II-4, Fig. 1)

The propositus was born at Curaçao (Dutch Antilles), after an uneventful term pregnancy and delivery. At birth, the eye and thumb abnormalities were noted. However, exact information on the initial eye findings is missing. No other major health problems occurred during childhood or puberty.

At the age of 23 years, he was investigated in our department for the first time. Height (171 cm) was at the 25th centile; weight (85 kg) and head circumference (OFC) (61 cm) were over the 98th centile. Except for eye abnormalities, no facial anomalies were present (Fig. 2). A hypoplastic thumb on right and an absent thumb on left were noticed (Fig. 3a). The left arm was about 6 cm shorter than the right. Furthermore, a sandal gap between the first and second toe and a partial cutaneous syndactyly between the second and third toe were present bilaterally. No abnormalities of the toenails were noted. Intelligence was normal.

Ophthalmological examination showed visual acuity of the right eye barely reaching light perception and of the left eye counting fingers at 2 m. A strabismus, nystagmus, bilateral microphthalmia, with microcornea (9 mm in diameter), cataract and iris coloboma, and left chorioideal coloboma involving the optical nerve were found. The fundus of the right eye could not be visualized because of the cataract. Hand films showed an absent thumb on left and absence of the os trapezoideum, hypoplasia of the os scaphoideum and os pisiforme, and fusion between the os lunatum and os triquetrum bilaterally (Fig. 3b). A skeletal survey showed no abnormalities, except for a somewhat short and curved humerus on left and absent posterior sacral arches. Abdominal ultrasound study showed absence of the right

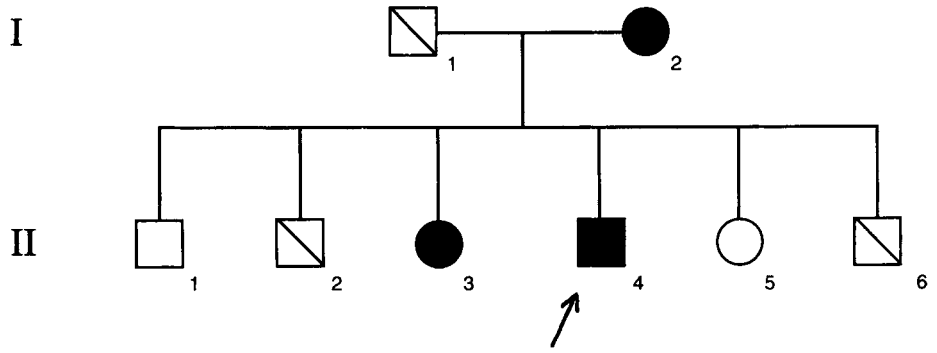

Fig. 1. Pedigree of the family. ■, Acro-renal-ocular syndrome. ⧅, Postaxial polydactyly.

kidney and a double system on left. Intravenous urography (IVU) showed a single enlarged left kidney containing a double pelvicalyceal system. The ureter originating from the proximal nondilated system had a downward course laterally to the kidney, was only distally dilated, and entered the bladder in a normal position. The ureter originating from the widened caudal crossed system ran downward on the medial side, curved across the midline, and entered the bladder somewhat high on the right side. This IVU fits with a left crossed ectopia with fusion (Fig. 4). Echocardiography showed no abnormalities.

Results of routine laboratory studies, including urine analysis, renal function tests, and blood counts, were all normal. Chromosome analysis showed a normal 46,XY karyotype.

Patient 2 (I-2, Fig. 1)

The mother of the propositus had hypoplasia of the left thumb. At 54 years, she underwent eye surgery because of presenile cataract, possibly due to diabetes mellitus type II. Ophthalmological examination in Curaçao did not show other defects, especially no microphthalmia or coloboma were present. No roentgenographic renal studies could be performed.

Patient 3 (II-3, Fig. 1)

A sister of the propositus was known with severe defects of the upper limbs, including absence of both thumbs, radii, and ulnae, short left humerus, contractures of the first finger on right, of the third and fourth finger on left, and syndactyly between the first and second finger on the left (Figs. 5, 6a,b). Ophthalmological examination at 25 years demonstrated visual acuity of 0.4 with slight myopic correction in both eyes. The anterior segments were normal with corneal diameters just within the normal range (10.25 mm). Fundoscopy showed slightly pale disks and chorioretinal scar tissue between the fovea and the optic nerve in both eyes. Sheathing of the major vessels pointed to an apparent past vasculitis. The patient reported rapid decrease in visual acuity 2 years earlier, in combination with a flu-like illness. Subjectively, the vision thereafter had slowly improved to the present state.

Patients 4, 5, and 6 (I-1, II-2, II-6, Fig. 1)

The father and two brothers of the propositus were said to have a postaxial polydactyly, without other abnormalities. Personal investigations have been impossible until now.

DISCUSSION

Our patient presented with upper limb, ocular, and renal anomalies. His mother and one of his five sibs also known had upper limb abnormalities. Acral defects in this family consisted of thumb hypoplasia or aplasia, carpal hypoplasia, absent radii and ulnae, humerus hypoplasia, contractures of interphalangeal joints, and II/III cutaneous syndactyly. The postaxial polydactyly in the father and the two sibs of the proband are probably unrelated. Ocular anomalies consisted of very poor visual acuity, strabismus, nystagmus, coloboma, cataract, and microphthalmia. Renal abnormalities consisted of renal ectopia, malrotation,

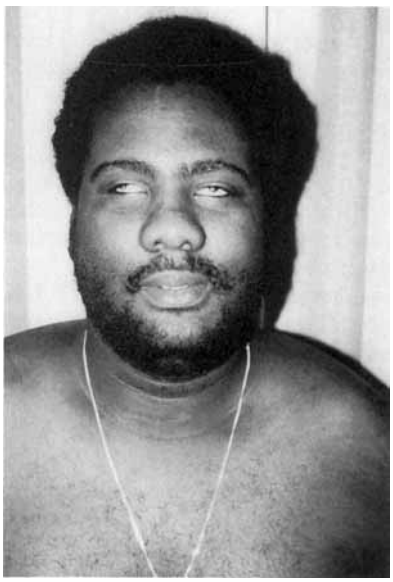

Fig. 2. Facial view of the proband; only eye abnormalities were present.

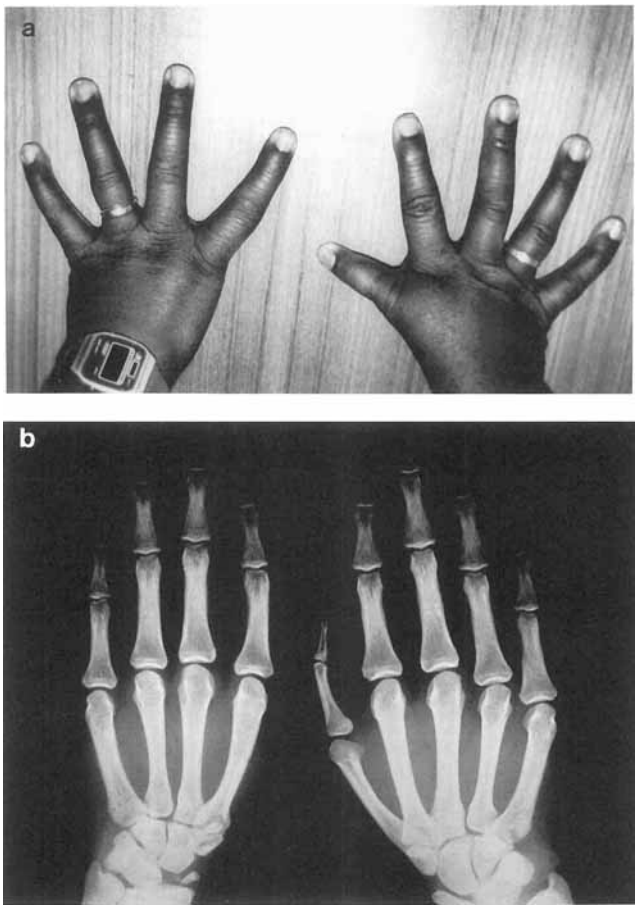

Fig. 3. **a,b:** Hands of the proband; note hypoplastic thumb on right and absent thumb on left.

Fig. 4. Intravenous urography showed left crossed ectopia with fusion.

and fusion. A similar triad of renal, ocular, and upper limb abnormalities has been reported before in four unrelated families by Temtamy and McKusick [1978], Halal et al. [1984], Naito et al. [1989], and Pierquin et al. [1991], respectively. Halal et al. [1984] were the first who recognized the triad as a distinct entity and named it the acro-renal-ocular syndrome. Clinical findings in these families are summarized in Table I. The mother of the patient described by Naito et al. [1989] suffered from repeated episodes of urinary tract infection and ophthalmoscopy showed coloboma of the choroid and optic nerve. Further information about this mother was not provided.

Thumb abnormalities, consisting of hypoplasia or aplasia in 12 and an extra thumb in two patients, have been reported in all affected persons and seem to be a consistent finding. However, selection bias for thumb abnormalities cannot be excluded. In order to avoid this bias, ocular and renal examinations of all relatives should have been performed. Unfortunately, for practical reasons, this appeared impossible in our family. Involvement of all parts of the upper limbs, with a wide range of severity, both interfamilial and intrafamilial appears possible. Embryologically, upper limb formation takes place between the fourth and eighth week of gestation.

Eye coloboma was reported in three families and Duane anomaly and microcornea in two. Our patient was the first case with congenital cataract. Both Duane anomaly and eye coloboma may have heterogeneous causes. However, the occurrence of Duane anomaly together with eye coloboma in one syndrome suggests a common genetic cause. Formation of the cranial nerves III, IV, VI, and their nuclei, and innervation of the extraocular muscles takes place between the fourth to eighth week of gestation. Closure of the optic fissure is completed by the eighth week of gestation. We consider the fundus abnormalities of patient 3 as coincidental.

Renal anomalies consisted of unilateral aplasia in three, renal ectopia in one, and malrotation in four families, respectively. Abnormal renal migration, therefore, seems to be a major cause of renal anomalies in this syndrome. Medial rotation and ascension of the kidneys from the pelvis to the abdomen mainly occur between the sixth to ninth week of gestation.

Variable vertebral anomalies were present in three families and ventricular septal defect, preauricular tags, choanal atresia, pulmonic stenosis, hearing loss, hiatal hernia, pilonidal sinus, and pectus excavatum have been reported in single cases.

Whether these manifestations are part of the syndrome or merely a coincidence remains to be seen. Normal intelligence was present in all affected persons, except for the patient described by Pierquin et al. [1991], who had a mild-to-moderate developmental delay. Other distinctive findings in this girl were unilateral cleft lip and palate and rib abnormalities, and the possibility of a distinct entity cannot be excluded.

Fig. 5. Frontal view of patient 3; note severe defects of the upper limbs.

A close embryological temporal relationship between Duane anomaly, eye coloboma, upper limb defect, and renal migration abnormalities, ranging from the fourth to the ninth week of gestation, supports the existence of a common (genetic) factor causing the various defects found in the acro-renal-ocular syndrome.

Autosomal dominant inheritance with variable expressivity seems to be present in all cases described until now. Dominantly inherited radial ray defects combined with the Duane anomaly have been reported several times as a separate entity [Ferrell et al., 1966; Okihiro et al., 1977; Hayes et al., 1985; McDermot and Winter, 1987]. However, in most reports no renal investigations were mentioned, which prevents distinguishing these cases from the acro-renal-ocular syndrome. Associated findings in these reports were cardiac anomalies [Ferrell et al., 1966], Hirschsprung disease and deafness [Okihiro et al., 1977; Hayes et al., 1985], cervical abnormalities [Hayes et al., 1985], and anal stenosis [McDermot and Winter, 1987].

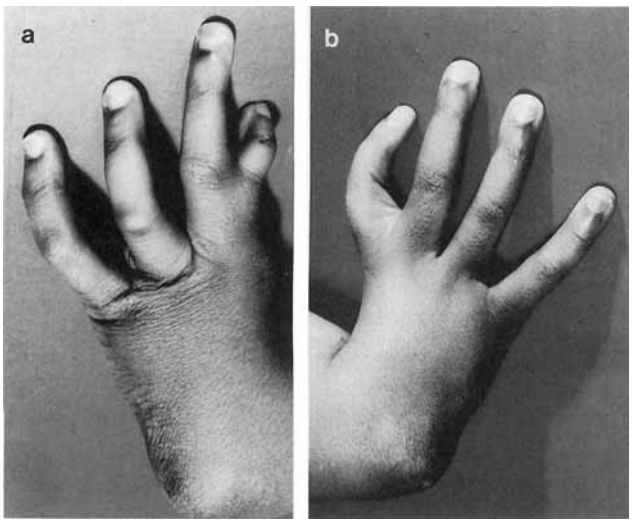

Fig. 6. **a,b:** Hands of patient 3; note thumb aplasia, contractures of fingers, and syndactyly.

Acral, ocular, and renal anomalies have been described in the Sorsby syndrome [Sorsby et al., 1935; Thompson and Baraitser, 1988]. Nine affected members in three subsequent generations of one family were reported. All nine had bilateral macular colobomas and apical dystrophy of hands and feet (brachydactyly type B), two had unilateral renal aplasia, and two others had mild to severe mixed hearing loss. Since the macular coloboma is not a true coloboma in the sense of an embryological closure defect, the ocular symptoms were different. The renal findings in this syndrome were similar to those in the acro-renal-ocular syndrome, but differed in that occurrence in the acro-renal-ocular syndrome was more variable. Furthermore, acral abnormalities differed, as brachydactyly type B was consistently present in the Sorsby syndrome.

A boy with severe psychomotor retardation, coloboma of the iris, split-hand and foot, left renal aplasia, and ventricular septal defect was described by Gehler and Grosse [1972]. Alsing and Christensen [1988] reported two sisters with coloboma, small kidneys, radiohumeral synostosis, dislocation of the hips, and hypoplasia of the fibulae. They later developed juvenile nephronophthisis and the diagnosis of the autosomal recessive Familial Juvenile Nephronophthisis was made. In the non-consanguineous parents, no history of renal, ocular, or skeletal disorder was present. Holmes and Borden [1974] described a boy with severe radial ray defects, consisting of absent thumbs, three fingers on the left hand and four on right, flexion deformities and ulnar deviation of fingers, and roentgenographically short radii. Other findings in this boy were ureteral reflux, a bladder diverticulum, urethral valves, left cryptorchidism, and a tuft of hair in the neck. Ocular abnormalities consisted of absence of the eyelashes on the medial half of the lower eyelids. No internal ocular defects were present. Whether the patterns of defects described by Gehler and Grosse [1972], Alsing and Christensen [1988], and Holmes and Borden [1974] are part of the acro-renal-ocular syndrome or not, remains to be determined.

Microphthalmia, renal hypoplasia, or aplasia and hypoplasia of the thumb are part of the Lenz microphthalmia syndrome [Traboulsi et al., 1988]. However, in this X-linked syndrome abnormalities and additional symptoms were more extensive than in the autosomal dominant acro-renal-ocular syndrome, which allows differentiation of the two syndromes.

In conclusion, the present family provides additional evidence for the existence of the acro-renal-ocular syndrome as a separate entity, with an autosomal dominant pattern of inheritance and wide variability. The major manifestations are upper limb anomalies, mainly thumb hypoplasia, eye abnormalities, mainly colo-

TABLE I. Summary of Findings in Five Reported Families With the Acro-Renal-Ocular Syndrome*

	Temtamy et al. [1978]		Halal et al. [1984]	Naito et al. [1989]		Pierquin et al. [1991]	Present family		
	1	2		1	2		1	2	3
Ocular									
Duane anomaly	−	+	+ (1/7)	−	−	−	−	−	−
Coloboma	−	−	+ (2/7)	+	+	+	+	−	−
Microcornea	−	−	+ (1/7)	−	−	−	+	−	−
Cataract	−	−	−	−	−	−	+	+	−
Strabismus	−	+	−	−	−	−	+	−	−
Nystagmus	−	−	+ (1/7)	+	−	−	+	−	−
Ptosis	−	−	+ (1/7)	−	−	−	−	−	−
Renal									
Malrotation	+	+	+ (2/7)	+		−	−		
Ectopia	−	−	+ (3/7)	−		−	−		
Unilateral aplasia	+	−	−	−		+	+		
Horseshoe kidney	−	+	−	−		−	−		
Vesicoureteral reflux	−	−	+ (2/7)	+		+	−		
Urinary tract infections	−	−	+ (4/7)	+	+	−	−	−	−
Acral									
Thumb hypoplasia/aplasia	+	+	+ (6/7)	−		+	+	+	+
Radius hypoplasia/aplasia	+	+	−	−		−	−	−	+
Ulna hypoplasia/aplasia	−	+	−	−		−	−	−	+
Humeral hypoplasia	−	+	+ (1/7)	−		−	+	−	+
Carpal hypoplasia	−	+	−	−		−	+	−	+
Preaxial polydactyly	−	−	+ (1/7)	+		−	−	−	−
Contracture	+	+	+ (5/7)	−		−	−	+	+
Cutaneous syndactyly	−	+	+ (1/7)	−		−	+	−	+
Dermatoglyphic abnormalities		+	+ (7/7)						
Other									
Mental retardation	−	−	−	−		+	−	−	−
Ventricular septal defect	−	−	−	+		−	−	−	−
Cleft lip/palate	−	−	−	−		+	−	−	−
Ear malformation	+	+	−	−		+	−	−	−
Preauricular tag	−	−	+ (1/7)	−		−	−	−	−
Congenital hearing loss	−	+	−	−		−	−	−	−
Choanal atresia	−	−	+ (1/7)	−		−	−	−	−
Vertebral abnormalities	−	+[a]	+ (1/7)[b]	−		+[c]	+[d]		
Pectus excavatum	−	+	−	−		−	−	−	−
Pulmonic stenosis	−	−	+ (1/7)	−		−	−	−	−
Hiatal hernia	−	−	+ (1/7)	−		−	−	−	−
Pilonidal sinus	−	−	+ (2/7)	−		−	−	−	−

*Clinical findings were absent (−) or present (+).
[a]Spondylosis of thoracic vertebrae.
[b]Spina bifida occulta C7, L5, S1.
[c]Absent anterior arch of atlas, malformed posterior arch C7.
[d]Absent posterior sacral arches.

boma, microphthalmia and Duane anomaly, and renal migration defects, which may lead to reflux or aplasia.

NOTE ADDED IN PROOF

Recently a mutation in the PAX2 gene in a family with optic nerve colobomas, vesicoureteral reflux, and renal anomalies was reported by Schimmenti et al. [Am J Med Genet 1995;59:204–208]. Although some differences in the eye and renal findings were present, and limb defects were absent in the family described by Schimmenti et al., molecular investigations for a similar mutation will be initiated in our family.

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